G(i)-coupled GPCR signaling controls the formation and organization of human pluripotent colonies.

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Public Summary:
Reprogramming adult human somatic cells to create human induced pluripotent stem (hiPS) cell colonies involves a dramatic morphological and organizational transition. These colonies are morphologically indistinguishable from those of pluripotent human embryonic stem (hES) cells. G protein-coupled receptors (GPCRs) are required in diverse developmental processes, but their role in pluripotent colony morphology and organization is unknown. We tested the hypothesis that G(i)-coupled GPCR signaling contributes to the characteristic morphology and organization of human pluripotent colonies. Experiments with pertussis toxin suggest that G(i) signaling plays a critical role in the morphology and organization of pluripotent colonies. These results may be explained by a G(i)-mediated density-sensing mechanism that propels the cells radially outward. GPCRs are a promising target for modulating the formation and organization of hiPS and hES cell colonies and may be important for understanding somatic cell reprogramming and for engineering pluripotent stem cells for therapeutic applications.

Scientific Abstract:
BACKGROUND: Reprogramming adult human somatic cells to create human induced pluripotent stem (hiPS) cell colonies involves a dramatic morphological and organizational transition. These colonies are morphologically indistinguishable from those of pluripotent human embryonic stem (hES) cells. G protein-coupled receptors (GPCRs) are required in diverse developmental processes, but their role in pluripotent colony morphology and organization is unknown. We tested the hypothesis that G(i)-coupled GPCR signaling contributes to the characteristic morphology and organization of human pluripotent colonies. METHODOLOGY/PRINCIPAL FINDINGS: Specific and irreversible inhibition of G(i)-coupled GPCR signaling by pertussis toxin markedly altered pluripotent colony morphology. Wild-type hES and hiPS cells formed monolayer colonies, but colonies treated with pertussis toxin retracted inward, adopting a dense, multi-layered conformation. The treated colonies were unable to reform after a scratch wound insult, whereas control colonies healed completely within 48 h. In contrast, activation of an alternative GPCR pathway, G(s)-coupled signaling, with cholera toxin did not affect colony morphology or the healing response. Pertussis toxin did not alter the proliferation, apoptosis or pluripotency of pluripotent stem cells. CONCLUSIONS/SIGNIFICANCE: Experiments with pertussis toxin suggest that G(i) signaling plays a critical role in the morphology and organization of pluripotent colonies. These results may be explained by a G(i)-mediated density-sensing mechanism that propels the cells radially outward. GPCRs are a promising target for modulating the formation and organization of hiPS and hES cell colonies and may be important for understanding somatic cell reprogramming and for engineering pluripotent stem cells for therapeutic applications.